

*B4  
B4  
Contd*

wherein said vitamin C is formulated in a slow-release preparation and vitamin E is formulated only in plain-release formulation;

wherein the concentration of vitamin E in the blood plasma is at least 20  $\mu$ mol/liter, and the concentration of vitamin C in the blood plasma is at least 40  $\mu$ mol/liter;

wherein the antioxidants are present in amounts so as to obtain vitamin C and vitamin E in a ratio in the blood plasma of 1:1 to 3:1;

wherein the at least one dosage units delivers a daily dose corresponding to 60 mg - 2 g of vitamin C and a daily dose corresponding to 50 mg - 500 mg of  $\alpha$ -tocopherol; and

wherein the formulation of vitamin E is such that at least 90% of vitamin E is dissolved in less than 30 minutes under the conditions of Test B, and the formulation of vitamin C is such that less than 40% of vitamin C is dissolved after 1 hour under the conditions of Test A.

*B5*

Add new claim 74 as follows:

-- 74. (New) A delivery system according to claim 38, substantially free of histidine.--

REMARKS

By this Amendment, claims 40-45, 51-56, 59, 61-66, 68, 72, and 73 are cancelled, claims 38, 39, 46-50, 57, and 67 are amended, and new claim 74 is added. Support for the amendments to the claims, and for new claim 74, comes from the specification and claims, as originally filed. Accordingly, no new matter is added by this Amendment. Currently, claims 38, 39, 46-50, 57, 58, 60, 67, 69-71, and 74 are pending and under consideration in this application.

I. *Rejection Under 35 U.S.C. § 112, first paragraph*

The Office rejects claims 57-66 under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description. (Office Action at paragraph 3.) Specifically, the Office rejects these claims for the failure of the specification to disclose diseases and disorders that have not yet been discovered. Applicants submit that the basis of the rejection is illogical. That is, it is impossible for Applicants to disclose diseases and disorders that have not yet been discovered. Indeed, Applicants are unaware of any relevant law or PTO rule that would (or could) require them to disclose diseases and disorders that have not yet been identified in order to satisfy the first paragraph of 35 U.S.C. § 112. In view of the fact that controlling law and PTO rules do not impose the impossible duty upon Applicants under 35 U.S.C. § 112, first paragraph, that the Office has imposed, Applicants submit that the rejection of claims 57-66 is improper, and should be withdrawn.

II. *Rejection Under 35 U.S.C. § 112, second paragraph*

The Office rejects claims 38-56 and 67-73 under 35 U.S.C. § 112, second paragraph, as "omnibus" claims. (Office Action at paragraphs 5 and 6.) Specifically, the Office asserts that it is not clear what is included or excluded from the claims. Applicants respectfully submit that the claimed subject matter is clearly defined by the present claims. For example, the claims specifically recite two vitamins to be delivered, the amounts of each to be achieved in blood plasma, and the ratio of the two to be delivered.

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The Office has not indicated why the claims are considered unclear (*i.e.*, identified any claim term that fails to clearly define the claimed subject matter). In the absence of any specific indication from the Office as to why the rejected claims might be considered unclear, Applicants cannot address this rejection to any further extent. Applicants request that the Office reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

### III. *Rejections Under 35 U.S.C. § 103*

The Office rejects claims 38-73 under 35 U.S.C. § 103(a) as unpatentable over Valducci in view of Hennekens, Thomas, Wakat, or Henriksen. (Office Action at paragraph 8.) Applicants respectfully traverse this rejection, and submit that the presently claimed invention is patentable over any combination of the cited references.

The present claims define a delivery system and a method of treating oxidative stress disorders that rely on: i) a slow release of vitamin C and a plain release of vitamin E; ii) in a specified amount of each of these vitamins, iii) to achieve a specific plasma ratio of these vitamins. None of the cited references describes a prolonged release of vitamin C and a plain release of vitamin E, or recognize the importance of obtaining a controlled ratio between vitamin C and vitamin E in order to treat oxidative stress diseases or disorders.

The Office appears to recognize that Valducci does not disclose a composition containing vitamin E in the amount recited in the present claims. The Office further appears to recognize that Valducci does not provide any motivation to increase the amount of vitamin E in the composition to achieve the presently claimed invention, or any reasonable expectation of

successfully achieving the presently claimed invention. However, the Office asserts that the secondary references provide motivation and a reasonable expectation of success. Applicants disagree.

Hennekens (US 5,871,766) discloses a method of inhibiting the occurrence of major vascular events by administrating  $\beta$ -carotene and/or vitamin E. Furthermore, Hennekens relates to a composition comprising  $\beta$ -carotene in combination with vitamin E. Hennekens recognizes the synergistic combination of the administration of  $\beta$ -carotene and vitamin E to a subject such that the occurrence of one or more vascular events is thereby reduced. Hennekens discloses daily doses comprising the combinations of 0.25 to 500 mg of  $\beta$ -carotene and 5 to 5000mg of vitamin E. However, Hennekens neither describes a prolonged release of vitamin C and a plain release of vitamin E, or recognizes the importance of obtaining a controlled ratio between vitamin C and vitamin E.

Thomas *et al.* (US 5,972,985) discloses compositions comprising histidine, which have antioxidant/free radical scavengers and cytoprotective effects. The compositions are combined with phytonutrients, such as vitamin C, E, and A, and  $\beta$ -carotene. Suitable compositions according to Thomas *et al.* comprise vitamin C or other antioxidants in the range of 0.0001 to 10 times the amount of histidine. Dosage units comprising histidine, vitamin C, and vitamin E in a weight ratio of approximately 2:2:1 to 1:1:1 (30mg:35mg:14mg to 20mg:20mg:20mg) are *implicitly* disclosed in example XI, XII, and XV. Thomas *et al.* neither describes a prolonged release of vitamin C and a plain release of vitamin E, or recognizes the importance of obtaining a controlled ratio between vitamin C and vitamin E. Moreover, although Thomas *et al.* discloses a

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composition comprising vitamin C and vitamin E in a 2:1 ratio, these vitamins are not in a prolonged release and plain release formulation. Furthermore, the amounts of the vitamins were in doses lower than the doses of the present invention, namely 60 mg-2 g and 50 mg to 500 mg.

Wakat (US 6,054,128) relates to dietary supplements comprising a combination of folic acid, vitamin B6, and B12, together with antioxidants to prevent or reduce the incidence of cardiovascular diseases. Vitamin C, vitamin E, and  $\beta$ -carotene are adjusted to provide maximum antioxidant effect. Compositions comprising 100 to 600 mg of vitamin C, 25 to 250 mg of vitamin E, and 800 to 1200  $\mu$ g of a retinol equivalent are disclosed.

Henriksen (US 6,136,859) discloses pharmaceutical formulations comprising organic or inorganic selenium,  $\beta$ -carotene, vitamin C, vitamin E, methionine, and coenzyme Q10 for treating liver disorders. The preferred compositions comprises 0.05 to 0.15 mg selenium, 3 to 5 mg  $\beta$ -carotene, 150 to 250 mg vitamin C, 40 to 87 mg vitamin E, 250 to 600 mg methionine, and from 25 to 50 mg coenzyme Q10.

While Wakat and the two Henriksen references disclose compositions comprising vitamin C and vitamin E in the same doses as the present invention, none of the cited references describes a prolonged release of vitamin C and a plain release of vitamin E, or recognizes the importance of obtaining a controlled ratio between vitamin C and vitamin E. In short, none of the cited references have recognized the need to have vitamin C and vitamin E within the ratio and dose level specifically defined by the present claims.

For at least this reason, Applicants submit that the cited references, alone or in combination, fail to have rendered the presently claimed invention obvious. Therefore,

Applicants request that the Office reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

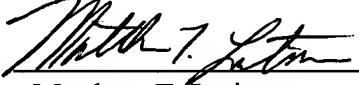
IV. *Conclusion*

If the Office believes anything further is necessary in order to place this application in even better condition for allowance, Applicants request that their undersigned representative be contacted at the telephone number or e-mail address below to discuss the remaining issues.

Please grant any extensions of time required to enter this Amendment, and charge any additional required fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Attachments:

Appendix  
Petition for Extension of Time

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